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(71) Applicant (*for all designated States except US*): SANDOZ GMBH [AT/AT]; Biochemiestrasse 10, A-6250 Kundl (AT).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): KREMMINGER, Peter [AT/AT]; Weitschön 86, 6250 Kundl (AT). WOLF, Siegfried [AT/AT]; Judenwiese 4a, 6230 Brixlegg (AT). LUDESCHER, Johannes [AT/AT]; Kleinsöll 101, A-6252 Breitenbach (AT).

(74) Agent: GRUBB, Philip; Novartis AG, Corporate Intellectuel Property, CH-4002 Basel (CH).

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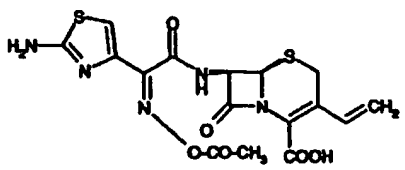
(54) Title: A CEFDINIR INTERMEDIATE



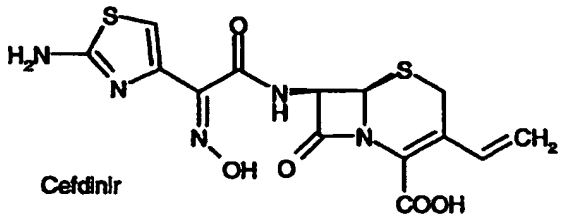
(I)

(57) Abstract: 7-[2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-cephem-4-carboxylic acid of formula (I), in the form of a crystalline salt and use thereof, e.g. in the preparation of pure cefdinir. In another aspect this invention relates to the compound of formula (I) in the form of a salt, optionally in crystalline form, wherein the salt is selected from the group consisting of phosphate, hydrogen phosphate, mesylate, tosylate, sulfate, hydrogen sulfate and sulfamate.

A CEFDINIR INTERMEDIATE

The present invention relates to organic compounds, in particular the compound (*6R,7R*)-7-[[(2*Z*)-(2-amino-4-thiazolyl)(hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (cefdinir). Cefdinir is an orally-administered cephalosporin with antibacterial properties, see e.g. The Merck Index Thirteenth Edition, Item 1933.

Production of cefdinir is not simple and cefdinir is not always obtained in sufficient purity. For example, it is known that the preparation of cefdinir of formula



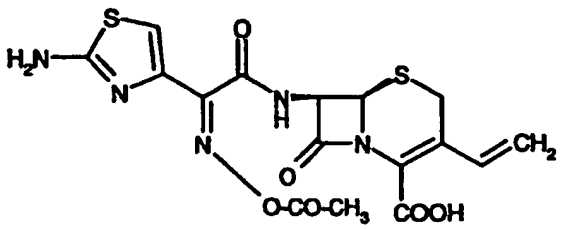
Cefdinir

may be carried out whereby the acyl side chain on the amino group in position 7 of the cephalosporin ring structure may be introduced in the form of a (reactive) acid derivative of the 7-side chain, in which the oxime group is protected by an acetyl protecting group, after which the acetyl protecting group is cleaved in order to obtain cefdinir.

Published international application WO 98/45299 discloses a method for purification of cefdinir by formation of a crystalline dicyclohexylamine salt.

Now, surprisingly, intermediates e.g. crystalline intermediates have been found in the production of cefdinir, from which very pure cefdinir may be obtained, so that production of highly pure cefdinir is simplified.

In one aspect, therefore, the present invention provides a compound of formula I



I

in the form of a crystalline salt.

It has surprisingly been found that the compound of formula I may be obtained in crystalline form in the form of a salt with a sulfonic or phosphonic acid or in the form of a salt with sulfuric acid, as hydrogen sulfate or sulfate.

In a further aspect, the present invention provides the compound of formula I in the form of a crystalline salt with a sulfonic or phosphonic acid, or in the form of a crystalline salt with sulfuric acid, as hydrogen sulfate or sulfate.

In another aspect this invention relates to the compound of formula I in the form of a salt, optionally in crystalline form, wherein the salt is selected from the group consisting of phosphate, hydrogen phosphate, mesylate, tosylate, sulfate, hydrogen sulfate and sulfamate. The new salts of this invention may be in pure or substantially pure form, for example displaying a purity of at least 90% by weight or more, e.g. 95% or greater, e.g. 98%, 99% or higher as determined by % HPLC area.

In the crystalline salts of the compound of formula I, the acid is preferably a sulfonic or phosphonic acid of formula II

$$R_1YO_3H \qquad II$$

in which R_1 signifies alkyl or optionally substituted aryl. Alkyl is preferably (C_{1-12})-alkyl, e.g. C_{1-6}-alkyl, for example methyl, ethyl or optionally branched (C_{3-12})-alkyl. Aryl is preferably, for example, phenyl, methylphenyl (toluol) or naphthyl. Alkyl and aryl includes unsubstituted and substituted aryl and alkyl, for example aryl substituted once or multiply by alkyl, for example (C_{1-6})alkyl, such as methyl, alkyloxy, e.g. (C_{1-6})-alkoxy, or nitro;

Y denotes S or P.

Examples of crystalline salts according to the invention include salts of the compound of formula I with an acid of formula HX, wherein X is a group Cl^-, HSO_4^-, ½ SO_4^{2-}, $H_2NSO_3^-$, $H_2PO_4^-$ and $R_1YO_3^-$, wherein R_1 and Y have the above-mentioned significances. Especially preferred salts include the hydrogen chloride, phosphate, sulfate, methane sulfonate, benzene sulfonate and toluene sulfonate of the compound of formula I.

Most preferred salts are phosphate, toluene sulfonate and benzene sulfonate.

The salts and crystalline salts of this invention are useful as intermediates, for example in the production of cefdinir.

Acetyl-cefdinir of formula I in salt form, e.g. as crystalline salt with sulfonic or phosphonic acid, sulfuric acid, sulfamic acid, phosphoric acid or hydrochloric acid according to the present invention is referred to herein as "cefdinir intermediate".

Cefdinir intermediates may contain crystal water or organic solvents bound therein. Cefdinir intermediates may therefore be present as such, or in the form of solvates, e.g. with organic solvents, or with water, for example in hydrated or partly hydrated form.

In another aspect, the present invention provides the compound of formula I in the form of a crystalline salt with a sulfonic- or phosphonic, sulfuric-, sulfamic-, phosphoric- or hydrochloric acid and in the form of a solvate, e.g. with an organic solvent or with water.

Crystallisation of the compound of formula I in the form of the salt according to one aspect of this invention, which is surprisingly successful, represents a purification step of high efficiency in production processes for the production of cefdinir. By preparing the cefdinir intermediate, cefdinir can be obtained in outstanding purity, e.g. >95% purity, e.g. 98% by weight, 99% by weight or higher, e.g. 99.5% by weight or higher, measured by % HPLC area. The content of impurities is very low, e.g. <5% by weight or less, e.g. 3% by weight, 2% by weight, 1% by weight or less, e.g. 0.5% by weight, or even less. Further, purification of cefdinir may be effected at an earlier stage of the cefdinir production process than only at the final cefdinir stage itself.

Cefdinir intermediates may be produced e.g. as follows

- Crystallisation by treating the compound of formula I in a solvent with H_2SO_4 , H_2NSO_3H, HCl, H_3PO_4 or an acid of formula II,
- Crystallisation by preparing the compound of formula I in silylated form and treating it in a solvent with H_2SO_4 , H_2NSO_3H, HCl, H_3PO_4 or an acid of formula II in the presence of H_2O, or in a silylatable protic solvent, e.g. an alcohol.
- Reaction of 7-amino-3-vinyl-3-cephem-4-carboxylic acid with a reactive derivative of *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid in a solvent which is inert towards the reaction conditions in order to produce the compound of formula I, and crystallisation by treating the reaction mixture in a solvent with H_2SO_4 , H_2NSO_3H, HCl, H_3PO_4 or an acid of formula II, optionally in a one-pot process.

Solvents which may typically be used for crystallisation may include e.g. alcohols, such as (C_{1-6})-alcohols, ketones, e.g. (C_{3-6})-ketones and ethers, for example tetrahydrofuran (THF), and mixtures of two or more of the said solvents, whereby water may optionally be present. Other solvents may be present, e.g. inert solvents which may be used in a process for the production of the compound of formula I, for example chlorinated hydrocarbons, such as CH_2Cl_2, nitriles, such as acetonitrile, and carboxylic acid esters, such as acetic acid-(C_{1-4})-alkyl esters.

To produce the cefdinir intermediate, the free base of the compound of formula I may be suspended in one of the said solvents or solvent mixtures, and crystallised by adding an acid of formula HX optionally in the presence of water.

The compound of formula I may be produced by known methods. Preparation may be carried out whereby 7-amino-3-vinyl-3-cephem-4-carboxylic acid in silylated form or as a salt with an amine or amidine or guanidine, e.g. DBU, DBN ,TMG, or a tertiary aliphatic amine, is reacted with a reactive derivative of *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid, for example *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid mercaptobenzothiazolyl ester, in a solvent which is inert towards the reaction conditions, e.g. as indicated above.

Production of the cefdinir intermediate may take place after isolating the compound of formula I in crystalline salt form from the reaction mixture, or in a one-pot process directly in the reaction mixture, by adding the acid of formula HX, in which X is defined as above, preferably in the presence of the solvent which may be used for crystallisation, as described above.

An equimolar amount of the compound of formula I and of the acid of formula HX may be used, whereby a slight excess of the acid, e.g. 1.1 to 1.5 molar equivalents of HX per equivalent of compound of formula I, may be of advantage. Higher excesses, for example two to five equivalents of acid, may also be used. If a trialkylammonium salt or an amidine or guanidine salt of 7-amino-3-vinyl-3-cephem-4-carboxylic acid is acylated, in order to obtain the cefdinir intermediate at least two molar equivalents of the acid of formula HX should be used. The amount of acid of formula HX which is to be used for crystallisation of the cefdinir intermediate therefore depends on the reaction conditions used for the production thereof.

In another embodiment the cefdinir intermediate may be obtained by adding the acid of formula HX to a suspension of the compound of formula I in a solvent, e.g. as described above.

In another embodiment, the cefdinir intermediate may be crystallised from a silylated compound of formula I by adding the corresponding acid of formula HX, e.g. the compound of formula I may be silylated by known methods, for example with N,O-bis-trimethylsilyl acetamide, N,O-bistrimethylsilyl trifluoroacetamide, monotrimethylsilyl-trifluoroacetamide, monotrimethylsilyl acetamide, hexamethyldisilazane or bis-trimethylsilyl urea, and an acid of formula HX is added under the conditions described above.

In general, special measures are not needed to desilylate the compound of formula I. For desilylation, generally the addition of the acid of formula HX and the addition of water or a silylatable protic solvent, e.g. an alcohol, are sufficient.

Cefdinir intermediates according to the present invention are especially suitable for producing cefdinir, since cefdinir may be obtained in high purity.

The production of cefdinir from cefdinir intermediates may be carried out for example by cleaving the acetyl protecting group on the oxygen of the oxime in the compound of formula I, whereby instead of the starting materials conventionally used, the cefdinir intermediate according to the present invention is used as starting material. The acetyl protecting group is unstable both in acids and in bases, so that this protecting group may be cleaved in an acidic or basic medium. In acidic medium, H_2SO_4 or sulfonic acids may be used e.g. as the acid, whereby cleavage may take place e.g. in an alcoholic or aqueous-alcoholic solvent medium.

Typically, cleavage of the acetyl protecting group may be carried out at a temperature of between -5°C and 15°C, for example between 0 and 10 °C.

In a basic medium, NH_3, NaOH or KOH or an alkaline earth carbonate, e.g. K_2CO_3, Na_2CO_3 or $NaHCO_3$, may be used e.g. as the base, whereby cleavage may take place e.g. in an aqueous or aqueous organic solvent. Basic medium, for example with a pH value of 7.5 – 9.5, e.g. 7.5-8.5 , is preferred.

Cefdinir may be crystallised in pure form from the reaction mixture, depending on the method used, by adding a base for cleavage in the acidic medium, or by adding an acid for cleavage in the basic medium.

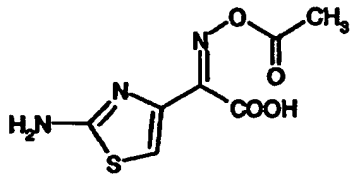
In another aspect, the present invention provides a process for the production of cefdinir, which is characterised in that

a) the compound of formula I is prepared in the form of the crystalline salt, optionally in form of a suspension, with a sulfonic- or phosphonic-, sulfuric-, sulfamic-, phosphoric- or hydrochloric acid,
b) the crystalline salt of the compound of formula I is converted into cefdinir by cleaving the acetyl group on the oxygen of the oxime, and
c) cefdinir is isolated, e.g. crystallised, from the reaction mixture of step b).

In another aspect, the present invention provides the use of the compound of formula I in the form of a crystalline salt for the production of cefdinir.

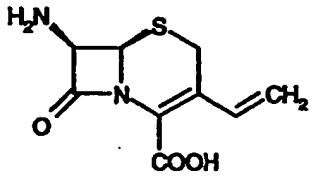
In a further aspect, the present invention provides a process for the production of cefdinir, which is characterised in that

a) a reactive derivative of the compound of formula III



III

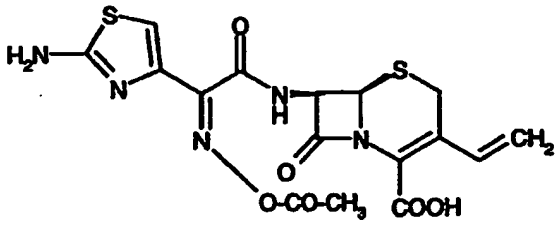
syn-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid, e.g. *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyl-oxyimino)-acetic acid mercapto-benzothiazolyl ester, is reacted with a compound of formula IV



IV

for example in reactive form, such as 7-amino-3-vinyl-3-cephem-4-carboxylic acid in silylated form,

to obtain the compound of formula I



I

(*6R,7R*)7-[[(*2Z*)-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-cephem-4-carboxylic acid, in which the carboxylic acid is optionally silylated,

b) acid HX, in which X is as defined above and R_1 is as defined above is added to the compound of formula I in order to obtain the crystalline salt of the compound of formula I with acid HX,

c) the crystalline salt from step b) is isolated,

d) the crystalline salt of the compound of formula I from step c) is converted into cefdinir by cleaving the acetyl group on the oxygen of the oxime, and

e) cefdinir is isolated from the reaction mixture of step d).

The reaction of the reactive derivative of the compound of formula III with the compound of formula IV may be carried out under aprotic conditions, e.g. in methylenechloride, acetonitrile or THF at a temperature of between 0 and 50°C, e.g. 20 to 40 °C.

In a further aspect, the invention provides a process for the production of *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid-mercaptobenzothiazolylester, in which the *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid is used as an ammonium salt, e.g. the tri-n-butylammonium salt, or an amine salt e.g. triethylamine salt.

In a further aspect, this invention provides a process for the production of the active ester, e.g. *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid-mercapto-benzothiazolylester, in which the compound of formula III is converted directly in water-moist form. "Water-moist" is understood to mean e.g. up to 50% by weight, e.g. 20 to 40% by weight water content.

Thus both a special drying step and isolation of the dry product are dispensed with, thereby making the process simpler and more economically attractive.

The above processes are simpler and more economically attractive than hitherto known processes.

In a further aspect, this invention provides a bulk quantity of cefdinir or cefdinir intermediate, for example 100 to 10,000 kg or more, e.g. 15,000 to 50,000 kg in high purity, which is produced by any of the above-described processes.

The following examples are intended to illustrate the invention more fully. Temperatures are indicated in °C and are uncorrected. The following abbreviations are used in the examples:

BSA	bis(trimethylsilyl)acetamide
BSU	bis(trimethylsilyl)urea
DMAc	N,N-dimethylacetamide
EtOH	ethanol
m.p.	melting point
HMDS	hexamethyldisilazane
MeOH	methanol
MsOH	methanesulphonic acid
RT	room temperature
TEA	triethylamine
TMSI	trimethylsilyl-iodide
TsOH	p-toluenesulphonic acid

X-ray diffraction measurements of salts of 7-[2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino) acetamido]-3-vinyl-3-cephem-4-carboxylic acid are summarised, respectively, in Tables 1 to 6 below and illustrated in Figures 1 to 6.

Example 1

(6R,7R)-7-[[(2Z)-(2-Amino-4-thiazolyl)(hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

A solution of 6.0 g of 7-[2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-cephem-4-carboxylic acid in the form of a salt with TsOH in 20 ml of MeOH is mixed at 0° with 1.05 ml of concentrated H_2SO_4, the mixture obtained is stirred at ≤10° and added dropwise to ca. 150 ml of an aqueous 3% $NaHCO_3$ solution. The pH value of the mixture obtained is adjusted to pH 5.0, 0.6 g of activated carbon are added, the mixture is stirred, and the activated carbon is filtered off and washed with H_2O. The filtrate obtained is heated to 25° to 30° and the pH value is adjusted to pH 3 with 2n H_2SO_4. (*6R,7R*)-7-[[(2Z)-(2-Amino-4-thiazolyl)(hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid crystallises, is filtered off, washed and dried. Weighed product: 3.09 g.

Example 2

***syn*-2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid-mercapto-benzothiazolylester**

10.0 g dried *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid (water content <1.0% by weight) are suspended at room temperature in 100 ml of methylene chloride and then cooled to 0°C. 11.3 ml of tributylamine are added dropwise over the course of 10 minutes, and stirring is then effected for 15 minutes. The solution is mixed with 18.6 g of bis-(benzothiazol-2-yl)-disulphide and stirred thoroughly for 5 minutes. In a period of 20 minutes, 9.7 ml of triethylphosphite are dispensed in and the solution is stirred vigorously for 1½ hours at 0°C, subsequently cooled to -20°C and stirred for a further 1½ hours. The yellowish crystalline product is filtered, washed three times, each time with 20 ml cold methylene chloride, and dried over night in a vacuum at 30°C.

Weighed product: 15.6 g

^{1}H-nmr(DMSO-d_6) δ2.22(s, 3H), 7.36(s, 1H), 7.48(br s, 2H), 7.59(m, 2H), 8.09(m, 1H), 8.22(m, 1H)

Example 3

***syn*-2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid-mercapto-benzothiazolylester**

20.0 g *syn*-2-(2-aminothiazol-4-yl)-2-(hydroxyimino)-acetic acid are suspended in 100 ml of water and dissolved by adding 23 ml of 5M sodium hydroxide solution. At a temperature of 20-28°C, 25.3 ml of acetic acid anhydride are slowly added dropwise, whereby the pH value of the solution is held at between 7.0 and 7.5 by simultaneously adding 5M sodium hydroxide solution. Afterwards, stirring is effected for 60 minutes at 25°C.

The solution is cooled to <10°C, and acidified to pH 3.0 over the course of 1 hour with 45 ml of conc. hydrochloric acid, whereby *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid crystallises. The mixture is stirred for 60 minutes at <5°C, filtered and washed 3x, each time with 30 ml of cold water.

The water-moistened product thus obtained is suspended in 250 ml of methylene chloride and heated under reflux using a water separator until the water content of the suspension is ≤0.05% by weight.

28.3 ml tributylamine are added at 0°C and stirring is effected for 15 minutes. The solution is mixed with 46.5g of bis-(benzothiazol-2-yl)-disulphide and stirred thoroughly for 5 minutes. After the addition of 24.3 ml of triethylphosphite, stirring is effected for 90 minutes, and then cooling is effected to -20°C. The mixture is stirred at this temperature for 90 minutes, then filtered and washed 3x, each time with 50 ml of cold methylene chloride. The material is dried over night at 30°C.

Weighed product: 30.0g

^{1}H-nmr(DMSO-d_6) δ 2.22(s, 3H), 7.36(s, 1H), 7.48(br s, 2H), 7.59(m, 2H), 8.08(m, 1H), 8.22(m, 1H)

Example 4

7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-cephem-4-carboxylic acid.hydrochloride

120.0g 3-vinyl-cephem-4-carboxylic acid are suspended in 1000ml dichloromethane and mixed with 167.1ml BSA at RT. The mixture is stirred for 2h and the clear solution obtained is cooled to 0°C. 147.6g *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetylchloride.hydrochloride are added over a period of / within 1h and the mixture stirred for 1h at 0°C. The mixture is cooled to –10°C and 69,9ml TEA are added dropwise. The cold reaction solution is added dropwise at RT over 1h to a mixture of 75ml water and 300ml MeOH. A suspension is formed which is stirred for 1h at 0°C. Crystalline product is filtered

off and washed twice, each time with 150ml cold methylene chloride. Isolated crystals are dried overnight at 35°C under vacuum.

Yield: 225.2g

^{1}H-nmr(DMSO-d_6) δ 2.21(s,3H), 3.61&3.88(ABq, 2H,J=17.6Hz), 5.24(d,1H,J=4.8Hz), 5.32(d,1H,J=11.4Hz), 5.60(d,1H,J=17.5Hz), 5.83(dd,1H,J=4.8&7.9Hz), 6.91(dd,1H,J=11.3&17.6Hz), 7.21(s,1H), 10.04(d,1H,J=7.9Hz)

HCl: 6.7%

m.p.: 140°C (decomposition)

Example 5

7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-cephem-4-carboxylic acid.methanesulfonate

5.0g 3-vinyl-cephem-4-carboxylic acid are suspended in 50ml dichloromethane and mixed with 5.87g BSU at RT. 20µl TMSI are added and the suspension is stirred for 2h. The suspension is filtered and the filter cake washed with 10ml methylenechloride. The combined filtrates are mixed with 10ml DMAc and 9,2g *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino) acetic acid-mercaptobenzthiazolylester are added in 1 portion at 30 °C. Stirring is continued for 2h at 30°C. The mixture is cooled down to 0°C and added dropwise to a solution of 1.9ml MsOH in 10.5ml EtOH and 2.4ml water. A thick suspension is formed which is diluted with 100ml methylenechloride followed by stirring for 30min at RT and for 1h at 0°C. Crystalline product is filtered off, washed three times, each time with 25ml cold methylenechloride, and dried at RT under vacuum.

Yield : 11.32g

^{1}H-nmr(DMSO-d_6) δ 2.21(s,3H), 2.41(s,3H), 3.61&3.88(ABq, 2H,J=17.7Hz), 5.24(d,1H,J=4.9Hz), 5.32(d,1H,J=11.4Hz), 5.61(d,1H,J=17.5Hz), 5.83(dd,1H,J=4.8&7.9Hz), 6.91(dd,1H,J=11.2&17.5Hz), 7.21(s,1H), 10.02(d,1H,J=7.9Hz)

CH_3SO_3H: 16.4%

m.p.: 170°C (decomposition)

Example 6

7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-cephem-4-carboxylic acid.*para*-toluenesulfonate

15.0g 3-vinyl-cephem-4-carboxylic acid are suspended in 150ml dichloromethane and the mixture heated to boiling. 13.6ml HMDS and 10µl TMSI are added and the mixture heated for 2h under reflux conditions and passing a nitrogen stream through the solution. The clear solution is cooled to 30°C and mixed with 30ml DMAc. 27.6g *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino) acetic acid -mercaptobenzthiazolylester is added in 1 portion and stirred for 3h at 30°C. The reaction mixture is added dropwise to a solution of 16.40g TsOH.hydrate in a mixture of 31.5ml EtOH and 7.2ml water. The product crystallizes out. The suspension is diluted with 360ml methylene chloride and stirred for 60min at 0°C. The crystalline product is filtered off and washed three times , each time with 75ml cold methylene chloride, and dried under vacuum at 30°C.

Yield: 39.32g

^{1}H-nmr(DMSO-d_6) δ 2.21(s,3H), 2.28(s,3H), 3.61&3.89(ABq, 2H,J=17.7Hz), 5.25(d,1H,J=4.8Hz), 5.32(d,1H,J=11.4Hz), 5.61(d,1H,J=17.5Hz), 5.84(dd,1H,J=4.8&7.9Hz), 6.92(dd,1H,J=11.1&17.4Hz), 7.12&7.48(AA'BB'm,4H), 7.22(s,1H), 10.04(d,1H,J=7.9Hz)

Toluenesulfonic acid: 26.0%

m.p.: 145°C (decomposition).

Example 7

7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-cephem-4-carboxylic acid.hydrogensulfate

5.0g 3-vinyl-cephem-4-carboxylic acid are suspended in 50ml dichloromethane, mixed with 7.1ml BSA at RT and stirred for 2h. The mixture is warmed to 30°C and 10ml DMAc and 9.2g *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid-mercaptobenzthiazolylester added. Stirring is continued for 2.7h at 30°C, the mixture cooled to 0°C, and a solution of 0.79ml concentrated sulfuric acid in a mixture of 10.5ml EtOH and 2.4ml water added dropwise. A suspension is formed which is diluted with 100ml methylenechloride, followed by stirring for 15min at RT and 1h at 0°C. The crystalline product is filtered off and washed twice, each time with 25ml cold methylenechloride and dried under vacuum at RT.

Yield: 10.58g

^{1}H-nmr(DMSO-d_6) δ 2.20(s,3H), 3.61&3.89(ABq, 2H,J=17.7Hz), 5.24(d,1H,J=4.8Hz), 5.32(d,1H,J=11.4Hz), 5.60(d,1H,J=17.5Hz), 5.83(dd,1H,J=4.8&7.9Hz), 6.91(dd,1H,J=11.2&17.5Hz), 7.17(s,1H), 10.00(d,1H,J=7.9Hz)

H_2SO_4: 10.7%

m.p.: 150°C decomposition

Example 8

7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-cephem-4-carbonic acid.sulfate

21.43g 3-vinyl-cephem-4-carboxylic acid are suspended in 214ml dichloromethane, mixed at RT with 15.68ml HMDS and 29µl TMSI, and heated under reflux for 2h and passing a nitrogen stream through the solution. The mixture is cooled to 30°C and 42.9ml DMAc and 39.4g *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid-mercaptobenzthiazolylester are added. Stirring is continued for 2.0 h at 30°C, cooled to 0°C and the reaction mixture added dropwise to a solution of 5.78ml conc. sulfuric acid in 53.6ml MeOH and 11.2ml water, on which a dense crystalline suspension is formed. Stirring is continued for 1h at 0°C, the mixture filtered and the recovered material washed three times, each time with 107ml cold methylene chloride, and dried under vacuum at RT.

Yield: 46.08g

^{1}H-nmr(DMSO-d_6) δ 2.20(s,3H), 3.61&3.89(ABq, 2H,J=17.7Hz), 5.24(d,1H,J=4.8Hz), 5.32(d,1H,J=11.4Hz), 5.61(d,1H,J=17.6Hz), 5.83(dd,1H,J=4.8&7.9Hz), 6.91(dd,1H,J=11.2&17.5Hz), 7.18(s,1H), 10.00(d,1H,J=7.9Hz)

H_2SO_4: 17.5%

m.p.: 170°C decomposition

Example 9

7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-cephem-4-carboxylic acid.phosphate

21.43g 3-vinyl-cephem-4-carboxylic acid are suspended in 214ml dichloromethane, mixed with 15.68ml HMDS and 29µl TMSI at RT and heated for 2h under reflux conditions and passing a nitrogen stream through the solution. The mixture is cooled to 30°C and 42.9ml DMAc and 39.4g *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid-mercaptobenzthiazolylester are added. The mixture is stirred for 2.0 h at 30°C, cooled to 0°C and the reaction mixture added dropwise at 0°C to a solution of 7.0ml 85% phosphoric acid in 53.6ml MeOH and 11.2ml water, on which a thick crystalline suspension is formed. The suspension is diluted with 257ml methylenechloride, stirred for 1h at 0°C and filtered. The filter cake is washed once with a mixture of 90ml methylenechloride and 17ml MeOH,

and then twice more, each time with 107ml methylenechloride, followed by vacuum drying at RT.

Yield: 42.60g

^{1}H-nmr(DMSO-d_6) δ 2.17(s,3H), 3.59&3.88(ABq, 2H,J=17.6Hz), 5.23(d,1H,J=4.8Hz), 5.31(d,1H,J=11.4Hz), 5.60(d,1H,J=17.5Hz), 5.82(dd,1H,J=4.8&8.0Hz), 6.90(dd,1H,J=11.2&17.6Hz), 7.08(s,1H), 9.91(d,1H,J=8.0Hz)

H_3PO_4: 16.9%

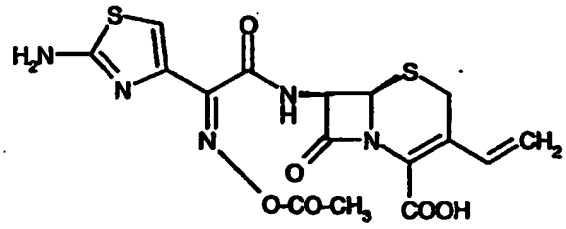
m.p.: 170°C (decomposition)

X-ray diffraction measurements

X-ray diffraction measurements are made of the phosphate, hydrochloride, tosylate, hydrogensulfate, mesylate and sulfate salts of 7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino) acetamido]-3-vinyl-3-cephem-4-carboxylic acid. The results obtained and diffraction patterns are shown respectively in the accompanying Tables 1 to 6 and Figures 1 to 6.

Claims

1. A compound of formula I



I

in the form of a crystalline salt.

2. A compound according to claim 1 in crystalline salt form, characterised in that the crystalline salt is a salt with a sulfonic or phosphonic acid or a salt with sulfuric or sulfamic acid, as the hydrogen sulfate, sulfate or sulfamate, or a salt with phosphoric acid, as the phosphate, or a salt with hydrochloric acid, as the hydrochloride.

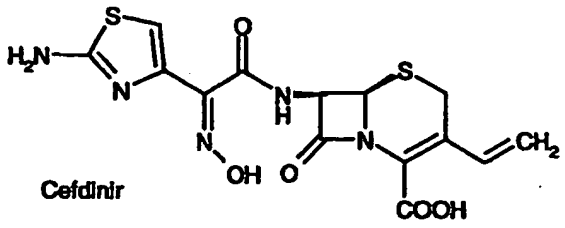
3. A compound according to claim 2, characterised in that the acid is an acid of formula II

HX II

in which X signifies Cl^-, HSO_4^-, $R_1YO_3^-$, $H_2NSO_3^-$, $H_2PO_4^-$, $½ (SO_4)^{2-}$ wherein
R_1 is alkyl or optionally substituted aryl and
Y signifies S or P.

4. A compound according to any one of claims 1 to 3, characterised in that the crystalline salt is a p-toluenesulfonate, methanesulfonate, hydrogen sulfate, sulfate, amidosulfate, phosphate, hydrogen chloride or benzenesulfonate.

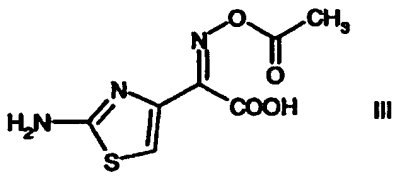
5. A process for producing the compound of formula



Cefdinir

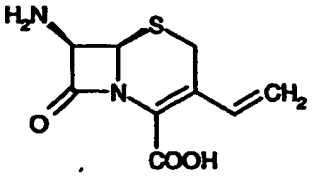
characterised in that

a) a reactive derivative of a compound of formula III



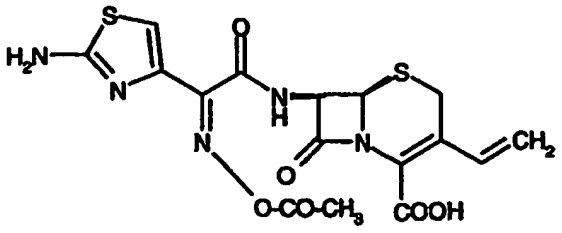
III

is reacted with the compound of formula IV



IV

to obtain the compound of formula I



I

b) an acid HX, in which
X signifies Cl^-, HSO_4^-, $H_2NSO_3^-$, $H_2PO_4^-$, ½ $(SO_4)^{2-}$ or $R_1YO_3^-$,
R_1 signifies alkyl or aryl and
Y is sulfur or phosphorous,
is added to the compound of formula I in order to obtain a crystalline salt of the compound of formula I with the acid HX,

c) the crystalline salt from step b) is isolated,

d) the compound of formula I in crystalline salt form from step c) is converted into cefdinir by cleaving the acetyl group on the oxygen of the oxime, and

e) cefdinir is isolated from the reaction mixture of step d).

6. A process according to claim 5, characterised in that *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid mercapto-benzothiazolylester is used as the reactive derivative of the compound of formula III.

7. Use of the compound of formula I in the form of a crystalline salt as claimed in any one of claims 1 to 4 for the production of cefdinir.

8. A bulk quantity of cefdinir having a purity of >99% by weight produced according to the process of claim 5 or 6.

9. A process for the production of *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid-mercaptobenzothiazolylester, wherein *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid is used as the tri-n-butylammonium salt.

10. A process for the production of *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid-mercaptobenzothiazolylester, wherein the compound of formula III is used in moist form.

11. A process according to claim 10, wherein the moist form contains up to 50% by weight water, e.g. 20 – 40% by weight water.

12. A compound of formula I in the form of a salt, optionally in crystalline form, wherein the salt is selected from the group consisting of phosphate, hydrogen phosphate, mesylate, tosylate, sulfate, hydrogen sulfate and sulfamate.

13. 7-[2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido-3-vinyl-cephem-4-carboxylic acid phosphate having an X-ray powder diffraction pattern substantially as that shown in Figure 1.

14. 7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-cephem-4-carboxylic acid hydrochloride having an X-ray powder diffraction pattern substantially as that shown in Figure 2.

15. 7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-cephem-4-carboxylic acid tosylate having an X-ray powder diffraction pattern substantially as that shown in Figure 3.

16. 7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-cephem-4-carboxylic acid hydrogensulfate having an X-ray powder diffraction pattern substantially as that shown in Figure 4.

17. 7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-cephem-4-carboxylic acid mesylate having an X-ray powder diffraction pattern substantially as that shown in Figure 5.

18. 7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-cephem-4-carboxylic acid sulfate having an X-ray powder diffraction pattern substantially as that shown in Figure 6.

19. A salt as claimed in any one of claims 12 to 18 in substantially pure form.

EVALUATION (D-SPACINGS, RELATIVE INTENSITIES) OF POWDER X-RAY DIFFRACTION PATTERNS

Equipment used

X-Ray Powder Diffractometer D-8 (AXS-BRUKER)
theta-theta-goniometer, sample changer
target: Copper, Kα1+Kα2 λ = 1.5406 Å
parallel beam optics (receiving soller-slit: 0.07 mm)
Scintillation counter, standard sample holders

Samples and Data-Collection

Table / Figure

1) 7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid- **phosphate**
data collection: 40kV, 40 mA, 2-40° θ/2θ, 0.01 steps, 2 seconds

2) 7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid- **hydrochloride**
data collection: 40kV, 40 mA, 2-40° θ/2θ, 0.01 steps, 2 seconds

3) 7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid- **tosylate**
data collection: 40kV, 40 mA, 2-40° θ/2θ, 0.01 steps, 2 seconds

4) 7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid- **hydrogensulfate**
data collection: 40kV, 40 mA, 2-40° θ/2θ, 0.01 steps, 2 seconds

5) 7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid- **mesylate**
data collection: 40kV, 40 mA, 2-40° θ/2θ, 0.01 steps, 2 seconds

6) 7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid- **sulfate**
data collection: 40kV, 40 mA, 2-40° θ/2θ, 0.01 steps, 2 seconds

external d-spacing standards:

1) NIST SRM 640A (Silicon Powder)
2) NIST SRM 675 (synth. Fluorophlogopite)
data collection: 40kV, 40mA, 2 - 50° θ/2θ, 0.01 steps, 2 seconds

Software

DIFFRAC-Plus and TOPAS (AXS-BRUKER)

External d-spacing and relative intensity evaluation of the powder diffractometer (D8 – AXS-BRUKER) with NIST standards:

SRM 640A:	$28.443°_{expected}$	$28.446°_{measured}$
	$47.304°_{expected}$	$47.308°_{measured}$
	Rel.Intensity $100_{expected}$	Rel. Intensity $100_{measured}$
	Rel.Intensity $55_{expected}$	Rel. Intensity $55_{measured}$
SRM 675:	$8.853°_{expected}$	$8.849°_{measured}$
	$17.759°_{expected}$	$17.754°_{measured}$
	$26.774°_{expected}$	$26.778°_{measured}$
	$35.962°_{expected}$	$35.962°_{measured}$
	$45.397°_{expected}$	$45.397°_{measured}$
	Rel.Intensity $81_{expected}$	Rel. Intensity $80_{measured}$
	Rel.Intensity $5_{expected}$	Rel. Intensity $5_{measured}$
	Rel.Intensity $100_{expected}$	Rel. Intensity $100_{measured}$
	Rel.Intensity $7_{expected}$	Rel. Intensity $6_{measured}$
	Rel.Intensity $28_{expected}$	Rel. Intensity $27_{measured}$

POWDER PATTERN (D-I-LIST)
7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid phosphate

Table 1

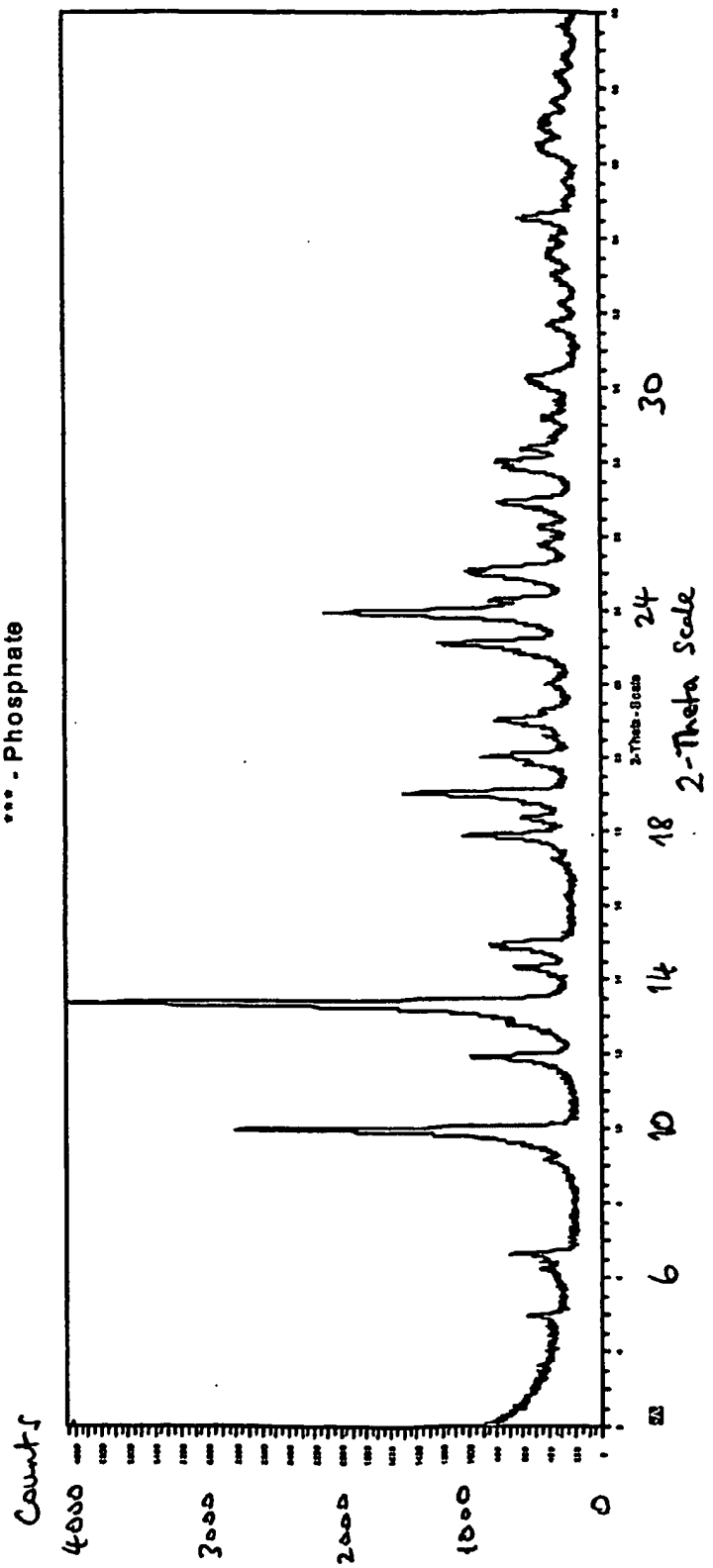
PHOSPHATE

d value (Angstrom)	Angle (° Cu Kα)	Intensity (Rel. Int.)
17.813	4.96	7
14.200	6.22	8
13.342	6.62	13
9.696	9.11	7
8.860	9.98	68
7.422	11.92	21
6.923	12.78	14
6.636	13.33	100
6.196	14.29	13
5.940	14.90	18
5.459	16.23	3
5.148	17.21	5
4.983	17.86	23
4.823	18.38	11
4.661	19.03	34
4.474	19.83	11
4.420	20.07	19
4.309	20.60	7
4.221	21.03	17
4.173	21.27	8
4.035	22.01	6
3.890	22.85	13
3.844	23.12	27
3.707	23.98	50
3.661	24.29	17
3.563	24.97	21
3.533	25.19	22
3.446	25.83	8
3.387	26.29	8
3.303	26.97	16
3.198	27.89	15
3.176	28.08	16
3.142	28.39	11
3.105	28.73	5
3.051	29.25	7
3.014	29.62	4
2.948	30.30	10
2.817	31.74	6
2.770	32.30	3
2.709	33.04	5
2.671	33.53	6
2.654	33.74	6
2.631	34.05	5
2.590	34.61	11
2.561	35.01	3
2.523	35.56	3
2.481	36.18	6
2.431	36.96	7
2.410	37.28	7
2.387	37.66	5
2.343	38.39	4
2.316	38.85	3
2.273	39.62	3

POWDER PATTERN (DIFFRACTOGRAMM) Figure 1

7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid -phosphate

*** - Phosphate



POWDER PATTERN (D-I-LIST)

7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid hydrochloride

Table 2

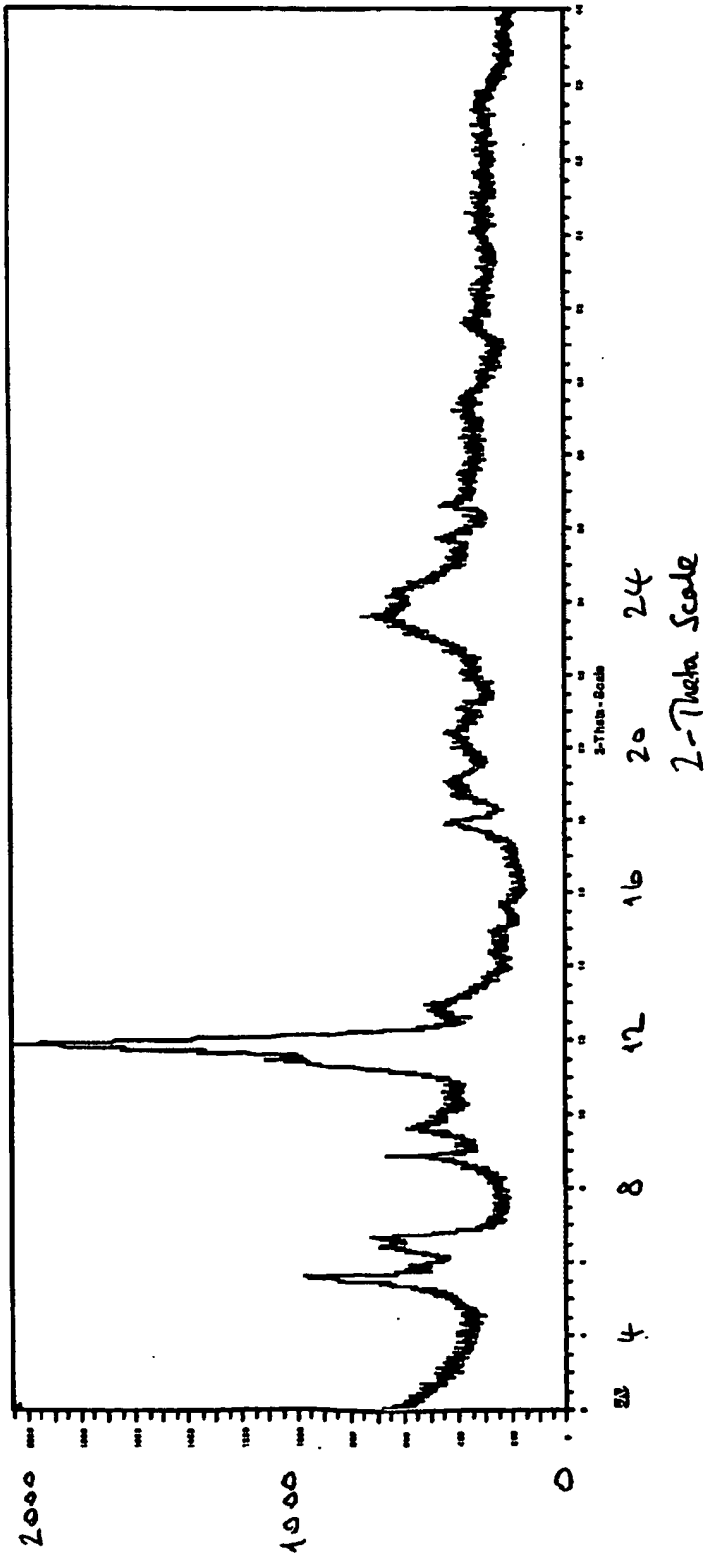
HYDROCHLORIDE

d value (Angstrom)	Angle (° Cu Kα)	Intensity (Rel. Int.)
15.934	5.54	36
15.176	5.82	18
13.791	6.40	23
13.281	6.65	25
9.965	8.87	24
9.171	9.64	20
7.720	11.45	48
7.460	11.85	100
6.825	12.96	17
6.129	14.44	6
5.940	14.90	8
5.661	15.64	5
4.963	17.86	14
4.744	18.69	13
4.648	19.09	13
4.406	20.14	11
4.328	20.51	13
4.197	21.16	10
4.040	21.98	8
3.760	23.65	27
3.670	24.23	22
3.454	25.77	11
3.348	26.60	11
3.238	27.52	7
3.057	29.19	7
3.017	29.59	7
2.830	31.59	7
2.752	32.51	6
2.631	34.05	6
2.404	37.38	7

POWDER PATTERN (DIFFRACTOGRAMM) Figure 2

7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid hydrochloride

*** - Hydrochloride



POWDER PATTERN (D-I-LIST)
7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid tosylate

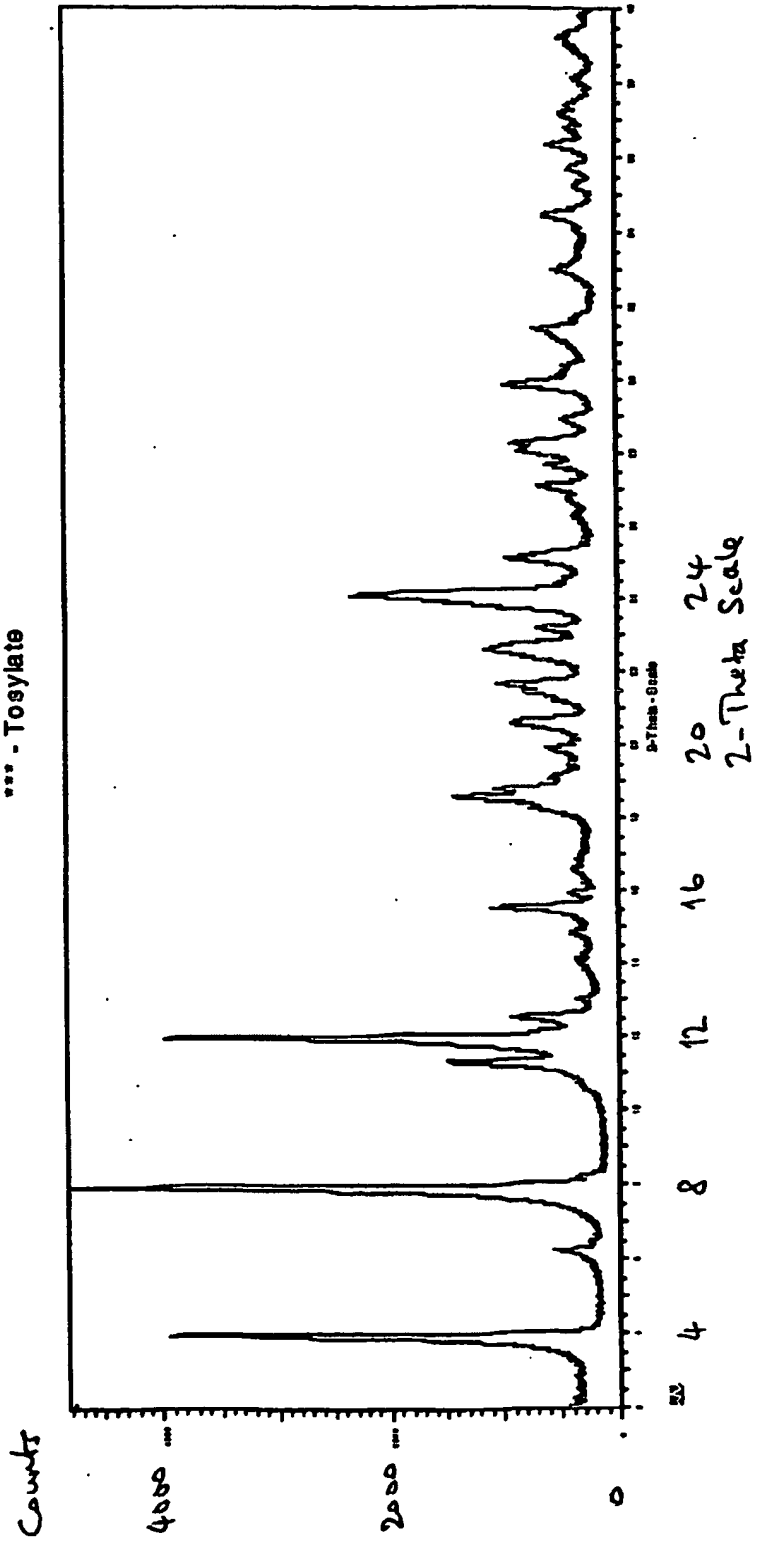
Table 3

TOSYLATE		
d value (Angstrom)	Angle (° Cu Kα)	Intensity (Rel. Int.)
22.579	3.91	80
14.130	6.25	9
13.660	6.47	3
11.185	7.91	100
10.747	8.22	5
8.322	10.62	4
7.826	11.30	28
7.403	11.95	61
7.041	12.56	16
6.777	13.05	4
6.289	14.07	4
5.977	14.81	5
5.696	15.55	19
5.563	15.95	5
5.328	16.63	4
4.947	18.29	11
4.776	18.57	26
4.714	18.81	18
4.631	19.15	8
4.480	19.89	8
4.309	20.60	14
4.143	21.43	12
4.097	21.68	17
3.926	22.63	19
3.824	23.25	10
3.717	23.92	28
3.689	24.11	45
3.542	25.12	15
3.383	26.32	3
3.329	26.76	4
3.289	27.09	9
3.213	27.74	9
3.176	28.08	13
3.146	28.36	15
3.086	28.91	8
2.989	29.86	16
2.957	30.20	6
2.938	30.42	5
2.888	31.16	8
2.844	31.43	11
2.822	31.68	4
2.714	32.97	7
2.671	33.53	3
2.628	34.08	4
2.589	34.49	9
2.542	35.28	3
2.510	35.75	5
2.471	36.33	8
2.439	36.82	5
2.417	37.16	6
2.400	37.44	5
2.381	38.09	4
2.305	39.04	5
2.293	39.26	6
2.258	39.90	2

POWDER PATTERN (DIFFRACTOGRAMM) Figure 3

7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid -tosylate

*** - Tosylate



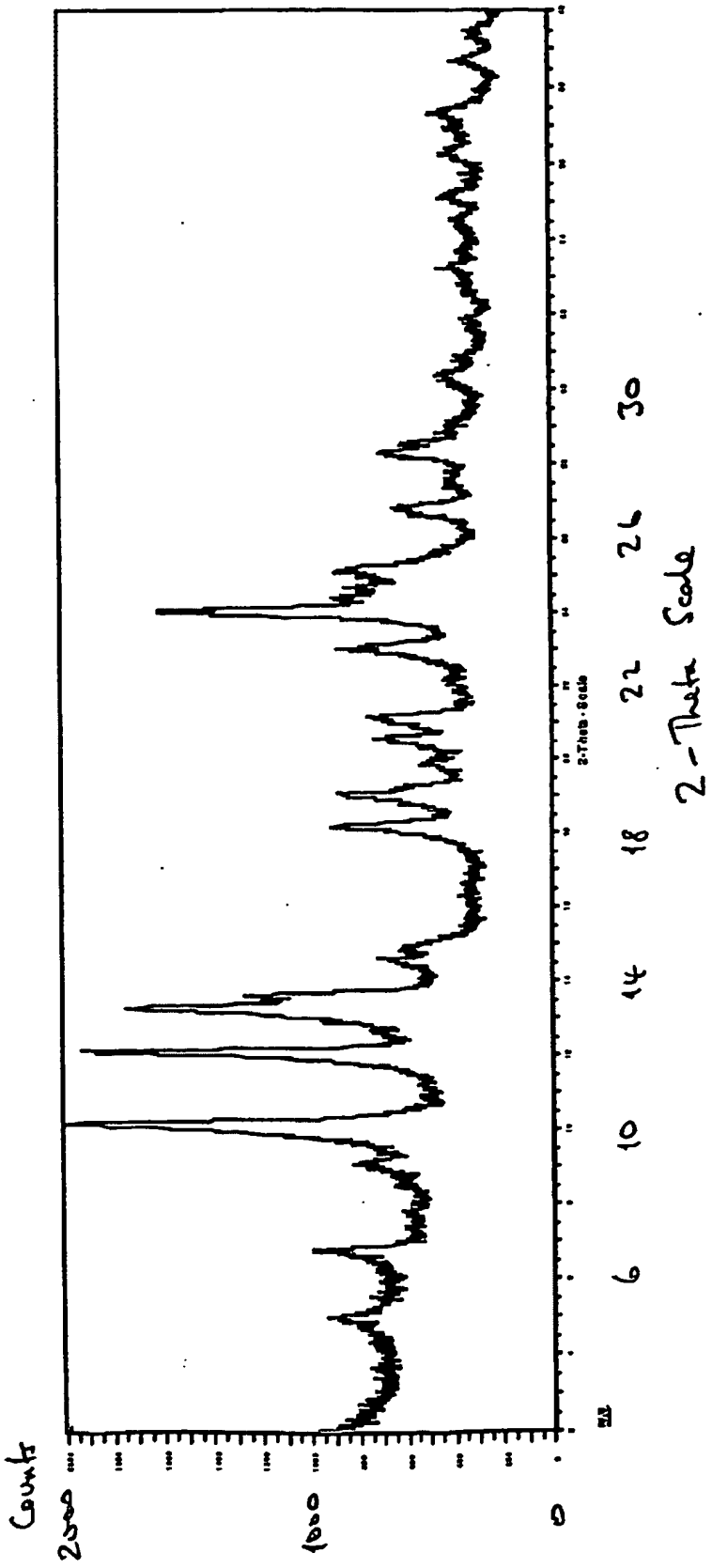
POWDER PATTERN (D-I-LIST)
7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid hydrogensulfate

Table 4

d value (Angstrom)	Angle (° Cu Kα)	Intensity (Rel. Int.)
18.863	4.68	12
17.700	4.99	21
13.037	6.78	28
9.793	9.02	20
8.751	10.10	100
7.289	12.13	98
6.681	13.24	88
6.515	13.58	56
6.089	14.54	24
5.939	14.90	19
4.887	18.14	39
4.652	19.06	36
4.480	19.80	14
4.321	20.54	24
4.214	21.06	26
4.017	22.11	6
3.868	22.97	35
3.697	24.05	82
3.647	24.39	37
3.602	24.70	32
3.533	25.19	36
3.325	26.79	21
3.230	27.59	7
3.151	28.30	26
3.121	28.58	20
3.085	28.92	9
2.944	30.33	11
2.901	30.79	7
2.803	31.90	6
2.729	32.80	8
2.692	33.26	11
2.658	33.72	9
2.594	34.55	10
2.554	35.11	13
2.476	36.25	14
2.433	36.92	14
2.407	37.32	17
2.321	38.77	11
2.279	39.51	9

POWDER PATTERN (DIFFRACTOGRAMM) Figure 4

7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid -hydrogensulfate



POWDER PATTERN (D-I-LIST)
7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid mesylate

Table 5

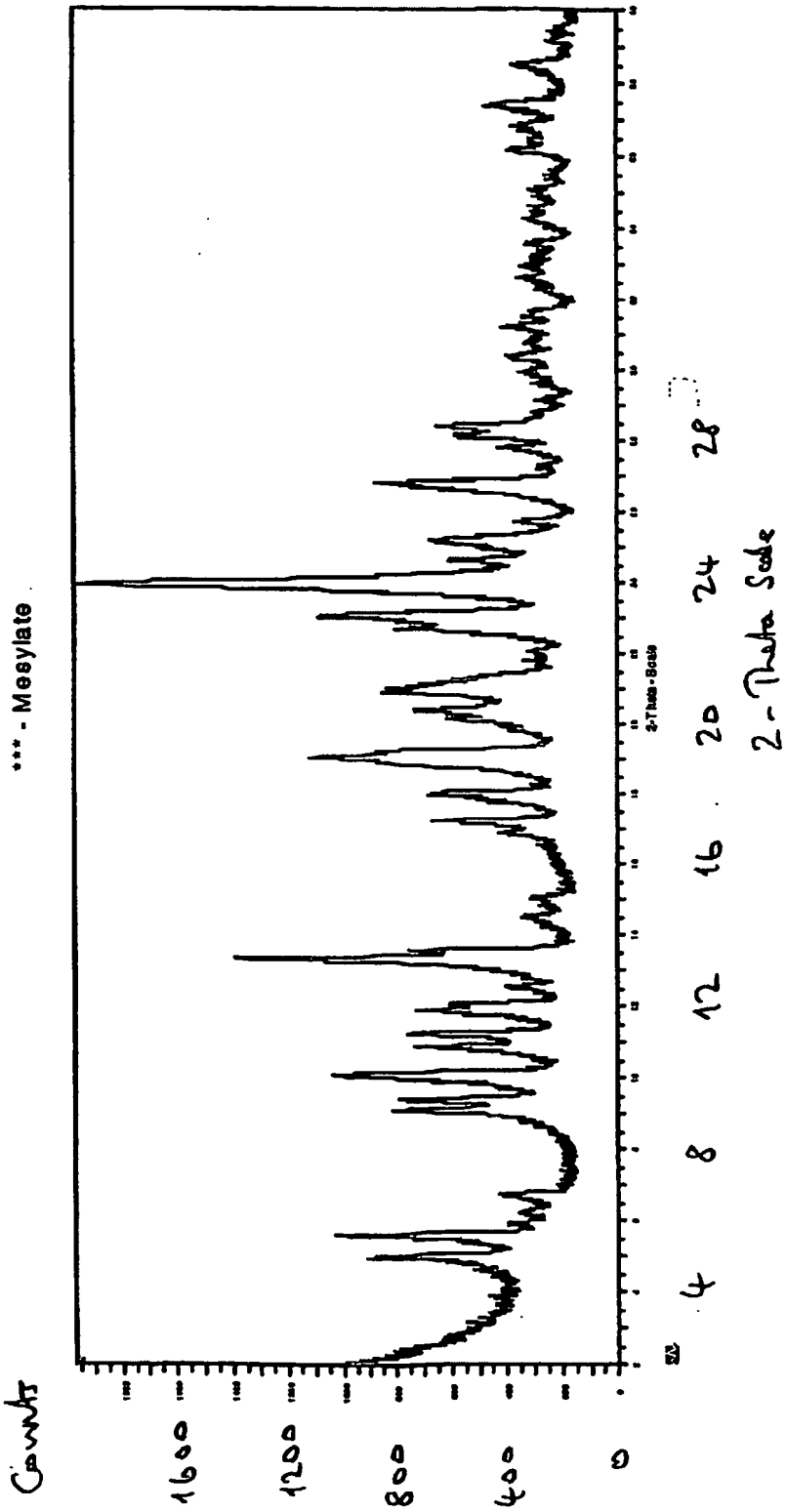
MESYLATE

d value (Angstrom)	Angle (° Cu Kα)	Intensity (Rel. Int.)
17.809	4.98	32
15.689	5.64	42
15.013	5.89	7
14.267	6.19	7
13.158	6.71	12
9.728	9.09	36
9.408	9.39	35
8.804	10.04	47
8.155	10.84	31
7.866	11.24	33
7.469	11.86	31
7.344	12.04	24
7.074	12.50	13
6.660	13.30	69
6.515	13.58	32
6.102	14.51	10
5.878	15.06	8
5.259	16.85	14
5.156	17.19	28
4.979	17.80	21
4.937	17.95	28
4.867	19.00	53
4.815	19.22	38
4.459	19.89	13
4.405	20.14	23
4.369	20.36	32
4.233	20.97	37
4.160	21.34	20
4.022	22.08	9
3.920	22.67	39
3.863	23.07	50
3.718	23.93	100
3.645	24.91	24
3.568	25.01	20
3.528	25.22	28
3.482	25.71	11
3.326	26.79	37
3.268	27.29	7
3.206	27.81	15
3.161	28.21	23
3.134	28.48	27
3.063	29.23	6
3.010	29.66	7
2.983	29.93	10
2.938	30.40	13
2.904	30.77	9
2.862	31.23	13
2.829	31.60	9
2.768	32.34	7
2.744	32.61	10
2.719	32.86	10
2.663	33.63	6
2.619	34.21	8
2.589	34.61	8
2.554	35.11	9
2.524	35.54	5
2.478	36.22	13
2.464	36.43	9
2.438	36.83	12
2.403	37.39	17
2.378	37.78	4
2.337	38.50	11
2.301	39.11	4
2.281	39.48	3

POWDER PATTERN (DIFFRACTOGRAMM) Figure 5

7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid -mesylate

*** - Mesylate



POWDER PATTERN (D-I-LIST)
7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid sulfate

Table 6

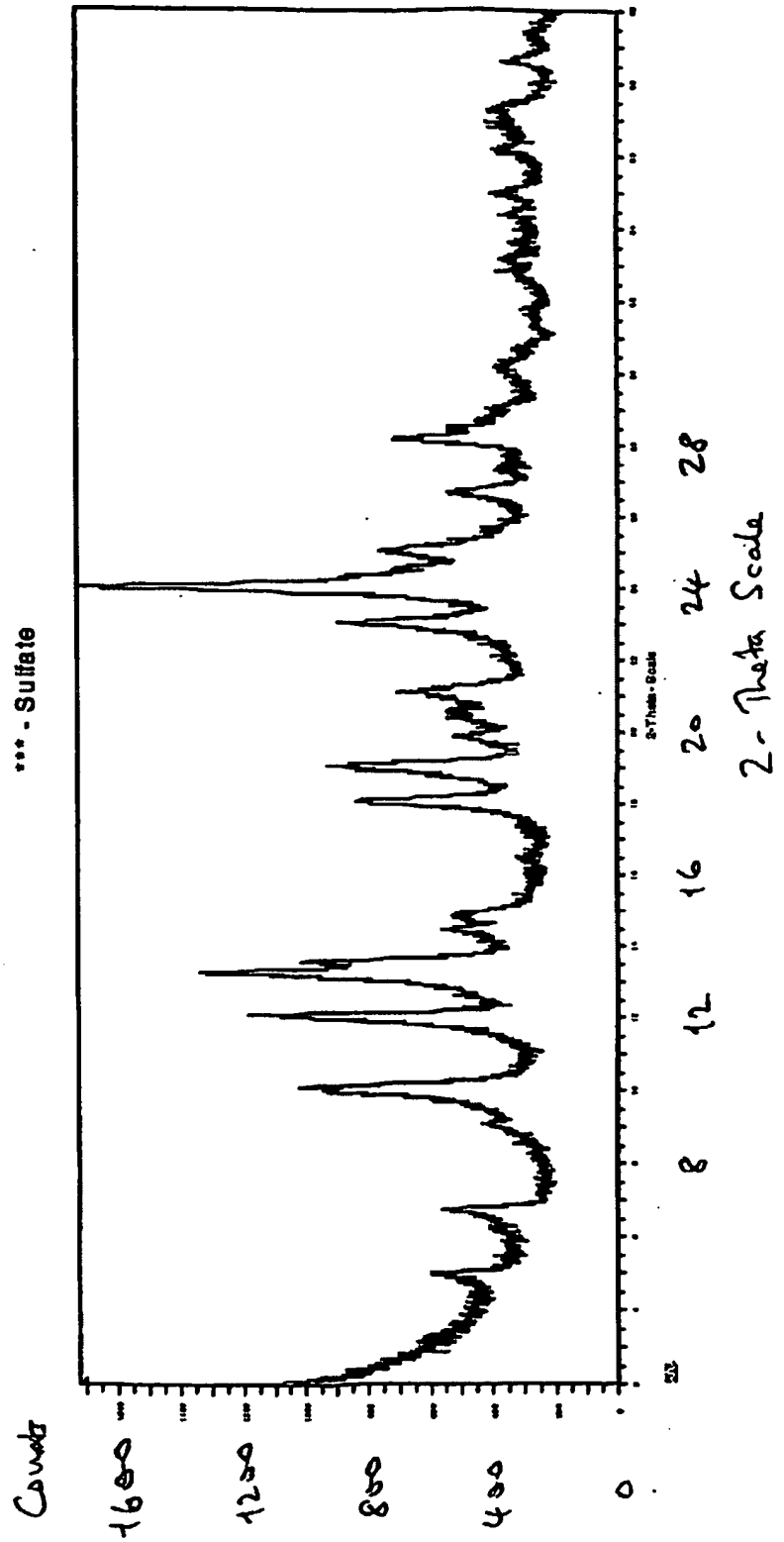
SULFATE

d value (Angstrom)	Angle (° Cu Ks)	Intensity (Rel. Int.)
17.824	4.93	15
13.099	6.74	20
9.795	9.02	12
8.808	10.04	48
7.346	12.04	63
6.667	13.27	72
6.548	13.52	51
6.103	14.50	21
5.953	14.87	19
5.377	16.47	6
4.888	18.13	39
4.661	19.03	45
4.467	19.86	19
4.328	20.51	21
4.203	21.12	32
3.859	23.03	44
3.698	24.05	100
3.616	24.60	32
3.542	25.12	35
3.467	25.68	13
3.333	26.72	21
3.245	27.46	11
3.158	28.23	33
3.125	28.54	21
3.070	29.06	12
2.954	30.23	10
2.907	30.73	7
2.844	31.43	3
2.814	31.77	5
2.722	32.88	8
2.695	33.22	10
2.659	33.69	7
2.603	34.42	9
2.561	35.01	11
2.493	36.15	10
2.435	36.88	12
2.408	37.32	14
2.327	38.67	9
2.288	39.35	5

POWDER PATTERN (DIFFRACTOGRAMM) Figure 6

7-[2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid -sulfate

*** - Sulfate



INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08944

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D501/00 A61K31/546

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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E	& EP 1 340 751 A 3 September 2003 (2003-09-03) Reference Examples I-(2) and I-(3) (For translation purposes)	1-19
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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
29 October 2003	04/11/2003

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3018

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Papathoma, S

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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